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January 23, 1956

Professor Joshua Lederberg
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Dear Josh:

It was very reassuring to find we were in agreement with you on so many points. Your summary at Detroit was masterful and constructive. The outline of the book is exciting. It reminds me that my often-interrupted project of summarizing the pathogenesis of each of the human hereditary diseases should be taken up again, perhaps as an encouragement to epigenetics to grow independently of the gene-product problem for a while.

Besides the several examples of tachyphylaxis or related phenomena in the pharmacological section of our review, there are some scattered ones: aspirin hydrolysis and reduced toxicity of betaine aldehyde, p.33, ref. 690 & 342; alcohol oxidation in kidney (still unconfirmed), p.37, ref. 418. Our mountain of cards contains no other useful ones except those referred to by Heilbrunn (ref. in footnote, p.1) and by L. C. Gunn in the only good review I have found ("Congenital and Acquired Tolerance to Non-Protein Substances" Physiol. Rev. 3, 41 (1923)). Mithridates and the Count of Monte Cristo provide the best examples.

Toxicity studies have undoubtedly turned up variations with a genetic basis, but these have usually been thrown out like the baby with the bath water. There is the stibophen reference, typically unpublished (p.106, ref. 84), and those cited by Gunn. Of course, galactose, phenylalanine and glucose, respectively, are "poisonous" to galactosemics, phenylketonurics, and patients with glycogen storage disease.

I suppose you are familiar with that gold mine of susceptibilities to disease called "Natural Resistance and Clinical Medicine" by Perla and Marmarston, (Little, Brown & Co., Boston, 1941). There are the phenomena awaiting explanation on either genetic or adaptive bases.

We were perhaps not as courageous as we should have been in explicitly redefining the words adaptation and induction. Their historical use, and our use of them, is to denote the physiological phenomena, not the hypothetical mechanisms by which these phenomena occur. On p.124 the

hypothetical mechanisms are labelled "speculative." Monod uses the expression "substrate-induced enzyme synthesis" to describe such a mechanism. That is his theory. We have been content with a physiological description of the phenomena, particularly since there is not yet sufficient information to make a theory of mechanism worthwhile.

Such a descriptive approach had its value, since it is now evident that the phenomenon was not correctly defined. I see from your comments that you reached the same conclusion. We believe the phenomenon is an up or down change in concentration of a specific protein. This occurs in response to a stimulus to the organism, and the response is conditioned by the metabolic state of the organism. These are good physiological concepts. We use the terms substrate- and hormone-induced adaptation, but we equate induction with stimulus. "Substrate-Regulation" is also good, but by itself it might be thought to neglect the role of the metabolic state. We recognize the reactions of protein synthesis and degradation at the root of the phenomenon. We can perceive that the mechanism of adaptation must involve the regulation of these reactions. The facts do not carry us beyond this, since we are blocked by our ignorance of specific protein synthesis. It is becoming clear, however, that a stimulus often acts indirectly through a chain or net of causation, and that the change induced has some metabolic consequences to the organism. The further definition of these aspects is a physiological problem which can be profitably studied.

Monod's "substrates which do not induce and inducers which are not substrates" really provide the "reductio ad absurdam" of the current ideas. Gale's review (your reference 6) and "basal" enzyme level variations reported since then (e.g. Wainwright's Nitratase) provide the evidence that the situation in microorganisms is similar to that which we found in animals, and was accurately described in your remarks.

It was a shocking thing, wasn't it, that the failure to observe β-galactosidase breakdown was considered a general and revolutionary finding by Cohn and Monod!

Sincerely,

Gene

W. Eugene Knox, M.D.